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EXTERNAL PREPARATIONS CONTAINING PROSTAGLANDIN E1

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Claims

1. External preparations containing prostaglandin E1, characterized by incorporating organic acids as stabilizers in compositions consisting of prostagladin E1, saturated fatty alcohols and glycols.

2. External preparations containing prostaglandin E1, characterized by incorporating organic acids as stabilizers in compositions consisting of prostaglandin E1, saturated fatty alcohols, glycols and absorption accelerators.

3. Ointment preparations containing prostaglandin E1, characterized by consisting of prostaglandin E1, saturated fatty alcohols, glycols and lactic acid and by adjusting the pH of the compositions to 3.0-5.0.

4. Ointment preparations containing prostaglandin E1, characterized by consisting of prostaglandin E1, saturated fatty alcohols, glycols, absorption accelerators and lactic acid and by adjusting the pH of the compositions to 3.0-5.0.

5. External preparations containing prostaglandin E1 of Claim 1, characterized by consisting of 0.0001-10 wt% prostaglandin E1, 15-45 wt% saturated fatty alcohols, 50-85 wt% glycols and 0.005-1.0 wt% organic acid and by adjusting the pH of the compositions to 3.0-5.0.

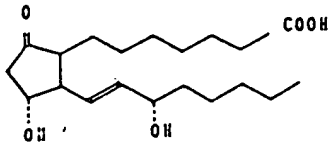
Detailed explanation of the invention

Industrial application field

This invention pertains to external preparations formed by containing prostaglandin E1 as the active component and having excellent stability and transdermal absorption property and drug efficacy.

Prior art

As shown in the structure below, prostaglandin E1 (hereafter, abbreviated as PGE1) is a compound of complex structure containing multifunctional groups in the molecule, including a double bond, hydroxyl groups or oxo groups. Moreover, PGE1 possesses various pharmacological activities even at microquantities, and it may be used as a thrombus treatment agent, antihypertensive agent, decubitus treatment agent, skin ulcer treatment agent, psoriasis treatment agent and hair growth drug.



However, as is obvious from the chemical structure shown above, PGE1 is in general a quite unstable compound, and is easily decomposed by acids, alkali, heat or light. Particularly, it undergoes a dehydration reaction in acidic conditions or under heating and converts to prostaglandin A1. Also, it is known to undergo isomerization under alkaline conditions and converts to prostaglandin B1.

Therefore, it is strongly desirable to improve the stability, especially over a long period of time, when PGE1 is utilized in drug preparation to produce pharmaceuticals. As such, there are many investigations attempting to stabilize the above said unstable compound PGE1. For

example, it has been known that there were compositions in which methylhesperidin was added as a stabilizer for prostaglandins (Japanese Kokai Patent Application No. Sho 53[1978]-127815), compositions in which citric acid esters were added (Japanese Kokai Patent Application No. Sho 53[1978]-127816), compositions in which phthalic acid esters were added (Japanese Kokai Patent Application No. Sho 53[1978]-127818), preparations using nonionic surfactants (for example, sorbitan monolaurate, sorbitan monopalmitate and sorbitan monostearate) (Japanese Kokai Patent Application No. Sho 53-148518), preparations incorporated with cellulose derivatives (Japanese Kokai Patent Application No. Sho 54[1979]-77497), medicinal materials containing silicone resins (Japanese Kokai Patent Application No. Sho 54[1979]-135495), compositions in which prostaglandins were incorporated into solvents containing specific propylene glycol diesters (Japanese Kokai Patent Application No. Sho 58[1983]-128325), and compositions which utilized etherified [sic; esterified] cyclodextrins for inclusion (Japanese Kokai Patent Application No. Sho 59[1984]-10525).

Problems to be solved by the invention

However, despite the fact that it is necessary to consider the stability of the drug preparations in particular when the unstable PGE1 showing useful pharmacological activity is used as a drug component in drug preparation, there has been insufficient investigation on the drug preparation for transdermal application, and there is no drug preparation with satisfactory stability, transdermal absorbing property and drug efficacy.

Means to solve the problems

Therefore, the present inventors had conducted vigorous investigations and many studies aiming at developing PGE1-containing external preparations that could solve the aforementioned various problems. That is, based on the conditions of incorporating PGE1 and having PGE1 stability over time, it was aimed at developing a formulation composition for an external vehicle having better stability and a drug formulation having good human transdermal absorption, and furthermore, the most optimum drug preparations that can be applied for treating subjects having target diseases. As a result, it was discovered that by incorporating organic acids, especially lactic acid, as stabilizers into certain ointment base vehicles, and by adjusting the pH of the preparations to the acidic region, the decomposition of PGE1 was significantly suppressed and all the aforementioned drawbacks were solved, achieving the present invention.

That is, the present invention provides target external preparations of PGE1 by incorporating PGE1 in base vehicles formed from saturated fatty alcohols, glycols and organic acids, and according to needs, absorption accelerators may be incorporated in the base vehicle.

To describe the present invention in more detail, the saturated fatty alcohols of the present invention are saturated fatty alcohols having 16-24 carbon atoms or their mixture and are preferably saturated monohydric primary alcohols. Among them, the particularly preferred ones are cetyl alcohol, stearyl alcohol and behenyl alcohol. Additionally, the saturated fatty alcohols are incorporated at 15-45 wt% based on the total weight, and preferably at 20-30 wt%.

The glycols are propylene glycol or butylene glycol (preferably 1,3-butylene glycol), and one or a mixture of two or more of these are utilized at 50-85 wt% based on the total weight, and preferably at 60-75 wt%. And, the organic acids are citric acid, succinic acid, tartaric acid, lactic acid, etc., and among them, lactic acid is the most preferred. Also, if the organic acids are incorporated in such a way that the pH of a 20% suspension of said composition is controlled in the acidic region, or more desirably within the range of 3.0-5.0, PGE1 can be further stabilized. The amount of incorporation is 0.005-1.0 wt%, and more preferably 0.01-0.5 wt%. Also, the active component PGE1 is incorporated at 0.0001-10 wt%, and preferably 0.001-1 wt%.

In addition to the aforementioned base vehicle and active components, it is desirable to incorporate absorption accelerators for the purpose of further promoting the absorption efficiency of the transdermal absorption. As the absorption accelerators, 1-dodecylazacycloheptan-2-one, 1-(2-(decylthio)ethyl)azacycloheptan-2-one, dimethyl sulfoxide, fatty alcohols such as lauryl alcohol or oleyl alcohol, crotamiton, fatty acids such as lauric acid or oleic acid, or terpenes such as l-menthol are utilized. The amount of application of the absorption accelerators is 0.01-8 wt% based on the total amount, and it is preferable that 0.1-5 wt% is incorporated.

Additionally, other additives may be incorporated according to needs including, for example, supplementary solvents (for example, polyethylene glycols having molecular weights of 100-800, glycerol, diethylene glycol monoethyl ether, propylene glycol monomethyl ether, dipropylene glycol monomethyl ether, 2,2-dimethyl-1,3-dioxolan-4-methanol, etc.) at under 25 wt%, plasticizers (for example, polyethylene glycols having molecular weights of 800-20,000, 1,2,6-hexanetriol, sorbitol, etc.) at under 15 wt%, coupling agents (for example, saturated fatty acids having carbon numbers of 16-24 such as stearic acid, palmitic acid, fatty acid amides such as oleamide, palmitamide, stearamide and behenamide, fatty acid esters having carbon number of 16-24 such as sorbitan monostearate, polyethylene glycol monstearate and propylene glycol monostearate, and other corresponding fatty acid esters of oleic acid and palmitic acid) at under 15 wt%. Also, the amount of incorporation of the aforementioned supplementary solvents and plasticizers is preferably at above 20 wt% for the drug preparation.

Moreover, it is preferable that, in addition to the aforementioned each vehicle, antioxidants (for examples, ethylenediaminetetraacetic acid, ether chelating agents, propyl gallate, butylated oxyanisole [sic; hydroxyanisole], etc.), surfactants, etc., are incorporated to further improve the stability of the drug preparation.

Next, in the production of the PGE1-containing ointment drug preparation of the present invention, saturated fatty alcohol (15-45 wt%), glycols (50-85 wt%), organic acids (0.005-1.0 wt%) and according to needs, absorption accelerator (0.01-8 wt%), or other additives are formulated and heated until dissolved at 80-95°C and mixed in the presence or absence of nitrogen gas.

Next, the mixture is cooled while mixing at room temperature. This is followed by incorporating active component PGE1(0.0001-10 wt%)-ethanol solution, mixing and agitating in the presence or absence of nitrogen gas, while controlling the pH in the acid region, and preferably in the pH range of 3.0-5.0 to produce the ointment drug preparation.

Application examples are carried out below to further describe the present invention more specifically.

Application Example 1

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.704 g and 1,3-butylene glycol 6.335 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Application Example 2

Stearyl alcohol 0.949 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.703 g and 1,3-butylene glycol 6.333 g as the glycols, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 5 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 3

Stearyl alcohol 0.949 g, cetyl alcohol 0.799 g and behenyl alcohol 0.899 g as the saturated fatty alcohols, propylene glycol 0.702 g and 1,3-butylene glycol 6.331 g as the glycols, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 10 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 4

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 7.039 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 5

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 2.112 g and 1,3-butylene glycol 4.927 g as the glycols, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Application Example 6

Stearyl alcohol 1.0 g, cetyl alcohol 0.5 g as the saturated fatty alcohols, propylene glycol 0.67 g and 1,3-butylene glycol 6.42 g as the glycols, PEG-6000 0.5 g and 1,2,6-hexanetriol 0.3 g as the plasticizers, sorbitan monostearate 0.2 g as the coupling agent, 1-dodecylazacycloheptan-2-one 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 100 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 7

Stearyl alcohol 2.5 g, cetyl alcohol 1.0 g and behenyl alcohol 1.0 g as the saturated fatty alcohols, propylene glycol 1.265 g and 1,3-butylene glycol 3.735 g as the glycols, 1,2,6-hexanetriol 0.10 g as the plasticizer, polyoxyethylene glycol monostearate 0.09 g as the coupling agent, 1-(2-(decylthio)ethyl)azacyclopentan-2-one 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 10 μg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 8

Stearyl alcohol 1.5 g as the saturated fatty alcohol, propylene glycol 3.4 g and 1,3-butylene glycol 5.095 g as the glycols, and lactic acid 0.005 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 100 μg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 9

Stearyl alcohol 2.0 g as the saturated fatty alcohol, 1,3-butylene glycol 6.595 g as the glycols, sorbitan monostearate 0.2 g as the coupling agent, PEG-6000 0.3 g as the plasticizer, oleic acid 0.8 g as the absorption accelerator and lactic acid 0.1 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 5 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 10

Stearyl alcohol 1.35 g, cetyl alcohol 1.0 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.609 g and 1,3-butylene glycol 5.29 g as the glycols, stearic acid 0.2 g as the coupling agent, PEG-6000 0.3 g as the plasticizer, l-menthol 0.3 g as the absorption accelerator and lactic acid 0.001 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 50 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 11

Stearyl alcohol 1.5 g, cetyl alcohol 1.0 g and behenyl alcohol 1.0 g as the saturated fatty alcohols, propylene glycol 2.264 g and 1,3-butylene glycol 3.735 g as the glycols, 1,2,6-hexanetriol 0.25 g as the plasticizer, polyethylene glycol monostearate 0.24 g as the coupling agent, and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Application Example 12

Stearyl alcohol 0.5 g and cetyl alcohol 0.5 g as the saturated fatty alcohols, propylene glycol 0.67 g and 1,3-butylene glycol 6.42 g as the glycols, PEG-6000 0.6 g and

1,2,6-hexanetriol 0.4 g as the plasticizers, sorbitan monostearate 0.3 g as the coupling agent and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 100 mg PGE1 are added and the composition is obtained by agitation and mixing.

Comparative Example 1

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.704 g and 1,3-butylene glycol 6.345 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Comparative Example 2

White petrolatum 8.299 g, bleached beeswax 0.8 g, stearyl alcohol 0.3 g, cholesterol 0.3 g and lauryl alcohol 0.3 g as the absorption accelerator are added together and heated to dissolve on a water bath by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Comparative Example 3

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.705 g and 1,3-butylene glycol 6.335 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation and mixing to obtain the composition.

Experimental Example 1 Stability test

In order to investigate the stability of PGE1 in the ointment drug preparations of the present invention, 2 g of each of the ointments of the Application Examples 1-10 and those of Comparative Examples 1-2 were filled in aluminum tubes coated with phenol resin on the inner side, and after storing for one month at 40°C in a constant-temperature oven, the residual amounts of prostaglandin were quantified by liquid chromatography. A column filled with octadecylsilylated silica was used for the liquid chromatography, and the moving phase was a mixed solution of 0.01M KH_2PO_4-acetonitrile, and the detection was conducted at 201 nm. The results are shown in Table 1.

Table 1

① 試　　料	② PGE1 残存率 (%)
実施例1の軟膏製剤	92.7
実施例2の軟膏製剤	92.4
実施例3の軟膏製剤	92.6
実施例4の軟膏製剤	91.8
実施例5の軟膏製剤	91.4
実施例6の軟膏製剤	90.9
実施例7の軟膏製剤	90.7
実施例8の軟膏製剤	91.0
実施例9の軟膏製剤	87.2
実施例10の軟膏製剤	90.2
比較例1の軟膏製剤	60.2
比較例2の軟膏製剤	28.9

③ ④

Key: 1 Sample
2 Residual rate
3 Ointment drug preparation of Application Example
4 Ointment drug preparation of Comparative Example

By comparing the results of the ointment drug preparations of the present invention to those of the Comparative Examples 1 and 2, it was found that the decomposition of PGE1 was significantly suppressed by adding lactic acid as a stabilizer.

Experimental Example 2 Test of skin blood flow rate

In order to confirm the localized efficacy of the ointment drug preparation of the present invention, determination of skin blood flow rate was conducted.

The compositions obtained in Application Examples 1, 2, and 3, and in Comparative Example 3 were applied openly at 5 mg each on a 1 x 1 cm area of the back skin of hairless mice anesthetized with urethane. The blood flow rate was determined before application and at 0.5, 1,

2, and 3 h after application, using a laser Doppler blood flowmeter. The differences before and after application were determined as Δv and used as the results, which are shown in Figure 1.

From the test results, it was found that the ointment drug preparations of the present invention showed significant increases of skin blood flow, compared to the case of Comparative Example 3 where PGE1 was not incorporated; additionally, it was found that the activity was maintained until 3 h after application, showing that the ointment drug preparation of the present invention was sufficiently absorbed transdermally while having sufficient drug efficacy.

Experimental Example 3 Transdermal testing

In order to confirm the transdermal absorption of the ointment drug preparation of the present invention by local application, determination of transdermal test of PGE1 was conducted.

A suitable amount of ^{3}H-PGE1 was added to the ointment drug preparations obtained in Application Examples 1, 4, and 5, and in Comparative Example 2 and mixed with agitation. Each ointment drug preparation was applied at 10 mg on the extracted back skin of hairless mice attached with a Loveday model diffusion cell. Physiological saline solution was used as the receptor phase, and a transdermal test was conducted at 25°C. The results are shown in Figure 2.

From the test results, it was found that the ointment drug preparations of the present invention showed significant transdermal absorption property, compared to the case of hydrophilic petrolatum of Comparative Example 2, and that the difference in transdermal absorption property was significantly affected by the difference in the ointment composition.

Function and effect of the invention

As is clear from the result of the aforementioned stability test, the ointment drug preparation of the present invention is extremely desirable because the drug composition can significantly inhibit PGE1 decomposition. Furthermore, the drug preparations are extremely stable so that they can be stored for a long period of time, and therefore, it is desirable for quality control purposes and is the most suitable for product commercialization. Additionally, the test of skin blood flow rate showed a significant increase of the skin blood rate and it was also found that the effect could be maintained for a few hours. This sufficiently underscores the fact that the ointment drug preparation of the present invention is smoothly absorbed transdermally, which results in the expression of the drug efficacy. Thus it is desirable for formulating drug preparations.

Additionally, in the transdermal testing, it showed significant transdermal absorption property, and it was found that the transdermal absorption property was markedly affected by the difference in the ointment compositions and that the results showed how superior the drug composition of the ointment of the present invention is.

Accordingly, the ointment drug preparation of the present invention is extremely superior on the stability of PGE1, the expression of the pharmacological activity and the transdermal absorption property. As an ointment drug preparation for the purpose of local application, it can be expected to be utilized in the treatment of Raynaud's disease, decubitus, skin ulcers, psoriasis, arteriosclerosis, etc., as well as being applied as a drug for hair growth.

Particularly, solving the problem of stabilizing PGE 1, which is the necessary condition for ointment drug preparation, is a matter of utmost importance in the drug preparation and is extremely useful to the pharmaceutical industry.

Bried description of the figures

Figure 1 shows the experimental results of skin blood flow when the drug preparation of the present invention was locally applied. The vertical axis shows the difference of blood flow rate before and after application of the compositions as Δv while the horizontal axis shows the lapsed time of the time course after application of the compositions.

Figure 2 shows the experimental results of the test of transdermal absorption when the drug preparation of the present invention was locally applied. The vertical axis shows the ratio of the amount of transdermal absorption of PGE1 to the amount of application, while the horizontal axis shows the lapsed time of the time course after the compositions are applied.

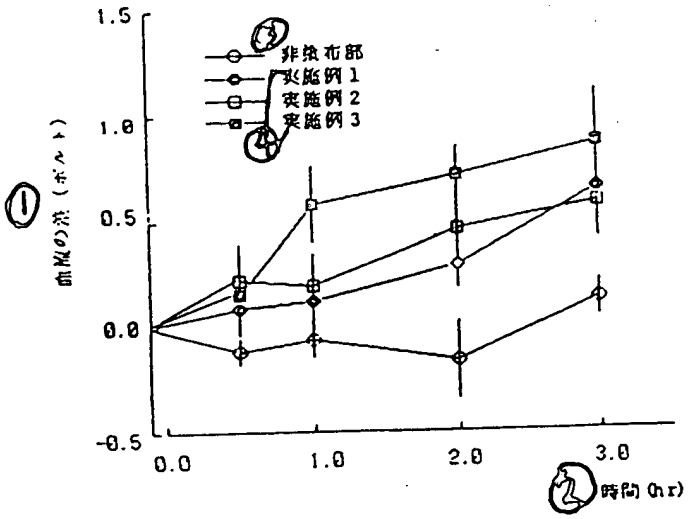


Figure 1

Key: 1 Difference in blood flow (volts)
2 Time
3 Nonapplied portion
4 Application Example

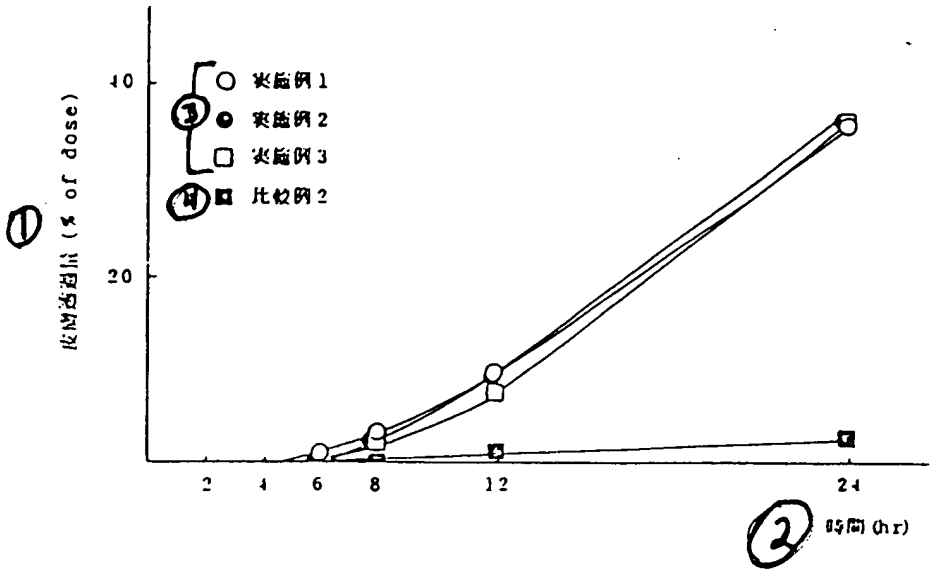


Figure 2

Key: 1 Amount of transdermal absorption
2 Time
3 Application Example
4 Comparative Example